CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-749

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-749 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Lamisil (terbinafine hydrochloride solution) Solution, 1% Action: (AP) AE NA

Applicant Novartis Pharmaceuticals Therapeutic Class 35

Indication(s) previously approved Interdigital Moccasin Type Tinea pedis, Tinea corporis, Tinea cruris, Onychomycosis

Pediatric labeling of approved indication(s) is adequate ✓ inadequate ___

Indication in this application tinea versicolor, tinea pedis, tinea cruris, tinea corporis

(For supplements, answer the following questions in relation to the proposed indication.)

X 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required. Safety & efficacy of this product has not been established in the pediatric population

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. →

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

_____ 9/5/97

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-749 10/9/97 10/17/97
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

With the exception of the largely self-limiting tinea corporis in prepubertal pediatric patients, all of the other tineas indicated are almost exclusively postpubertal and are qualitatively similar to the adult conditions. The safety should also be the same for postpubertal pediatric patients and adult patients.

10/17/97

LAMISIL® Solution 1% (terbinafine hydrochloride solution)
New Drug Application

SANDOZ CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

SANDOZ PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

10/11/96
Date

Michael S. Perry, DVM, PhD
Vice President
Drug Registration and Regulatory Affairs

13. PATENT INFORMATION

Lamisil® (terbinafine hydrochloride) is covered by United States Patent 4,680,291 (issued July 14, 1987 and expiring on July 14, 2004) and United States Patent 4,755,534 (issued July 5, 1988 and, in view of a 543 day extension, expiring on December 30, 2006). Both of these patents cover terbinafine hydrochloride, pharmaceutical compositions containing the drug (including solutions), and its use as an antimycotic agent.

Federal Register

Thursday
July 22, 1993

JONATHAN K. WILKIN, M.D.

Part VI

Department of Health and Human Services

Food and Drug Administration

Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93D-0236]

Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a guideline entitled "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." This guideline provides new guidance on FDA's expectations regarding inclusion of both genders in drug development and revises the section "Women of Childbearing Potential" in the 1977 guideline entitled, "General Considerations for the Clinical Evaluation of Drugs" (HEW Publication No. (FDA) 77-3040).

DATES: Written comments by November 19, 1993.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857. Copies of this notice, which includes the text of the new guideline, and of the other guidelines mentioned in this document, are available from the Center for Drug Evaluation and Research (HFD-8), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send two self-addressed adhesive labels to assist that office in processing your requests.

FOR FURTHER INFORMATION CONTACT: Patrick J. Savino, CDER Executive Secretariat Staff (HFD-8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8012.

SUPPLEMENTARY INFORMATION:

I. Introduction

In this document, FDA is publishing a new guideline on FDA's expectations regarding inclusion of patients of both genders in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and conduct of specific additional studies in women, where indicated. This guideline revises the section of the 1977 guideline, entitled "General Considerations for the Clinical Evaluation of Drugs," that excluded women of childbearing potential from participation in early studies of drugs. For the purpose of this document, the agency will refer to the "General Considerations for the Clinical Evaluation of Drugs" as the "1977 guideline."

Although the new guideline outlines in some detail the specific considerations related to the evaluation of gender differences during evaluation of drug products, the agency views the principles of inclusion of women in product development programs and analysis of subgroup differences as being broader standards which apply equally to the clinical development of biological products and medical devices.

The new guideline reflects good drug development practice implicit in the law and regulations. Certain requirements, such as inclusion of adequate numbers of women and by-gender analyses, have been emphasized in the past. However, as with any new guideline, where sponsors have developed drugs in good faith relying on existing guidelines, they will have an opportunity to satisfy newly appreciated data needs after approval where this is compatible with the public health and the law. This new guideline does not change FDA's commitment to safe development of drugs but gives more flexibility to institutional review boards (IRB's), investigators, and patients in determining how best to ensure safety.

II. Background

A. Participation of Women in Clinical Studies

Over the past decade there has been growing concern that the drug development process does not produce adequate information about the effects of drugs in women. This concern arises from a number of sources.

Analyses of published clinical trials in certain therapeutic areas (notably cardiovascular disease) have indicated that there had been little or no participation of women in many of the studies. Certain major studies of the role of aspirin in cardiovascular and cerebrovascular disease, for example, did not include women, and this omission left the scientific community with doubts about whether aspirin was, in fact, effective in women for these indications. Similarly, published studies of anti-anginal drugs often had few or no women in them. It has been suggested that a similar situation might exist for the studies intended to support marketing approval of new drugs.

In addition, FDA notes that there has been little study of the effects of such aspects of female physiology as the menstrual cycle and menopause, or of the effects of drugs widely used in women such as oral contraceptives and systemic progestins and estrogens, on drug action and pharmacokinetics.

Concern has also been expressed that the 1977 policy excluding women of childbearing potential from early drug studies may have led to a more general lack of participation of women in drug development studies, and thus to a paucity of information about the effects of drugs in women. In addition to concerns about whether the policy interfered with development of adequate data on drug therapy in women, the 1977 guideline, seen from the viewpoint of the 1990's, has appeared rigid and paternalistic, leaving virtually no room for the exercise of judgment by responsible female research subjects, physician investigators, and IRB's.

Concerns about the adequacy of data on the effects of drugs in women have arisen at a time when FDA, drug developers, and the scientific community have focused increasingly on the need to individualize treatment in the face of the wide variety of demographic, disease-related, and individual patient-related factors that can lead to different responses to drugs in subsets of the population. Optimal use of drugs requires identification of these factors so that appropriate adjustments in dose, concomitant therapy, or monitoring can be made.

Subgroup-specific differences in response can arise because of variation in a drug's pharmacokinetics (i.e., the drug's concentration in plasma or elsewhere as a function of time) or pharmacodynamics (the body's response to a given concentration of the drug).

B. Pharmacokinetic and Pharmacodynamic Differences Among Patients

Important variations in pharmacokinetics can arise from many factors:

1. A number of demographic characteristics may affect pharmacokinetics: Older people are more likely to have decreased renal function, which may cause drugs excreted by the kidney to accumulate; younger people metabolize theophylline more rapidly; ethnic groups differ in the prevalence of metabolic abnormalities such as slow acetylation and G6PD deficiency; women metabolize certain substances at rates different from men (for example, they metabolize alcohol and ondansetron more slowly).

2. Diseases other than the one being studied may alter the pharmacokinetics of many drugs: Kidney disease may decrease the ability to excrete drugs in

the urine; liver disease can interfere with the metabolism of drugs or with their excretion into the bile.

3. The presence of other drugs may lead to pharmacokinetic interactions: Quinidine and fluoxetine inhibit the metabolism of imipramine and desipramine, as well as that of many other drugs metabolized by cytochrome P450 2D6 (debrisoquin hydroxylase); ketoconazole and erythromycin inhibit the metabolism of terfenadine. In such cases, toxic blood concentrations of the drug whose metabolism is inhibited can occur even while a constant dose of the drug is maintained.

4. In addition, other differences between individual subjects may affect pharmacokinetics. For example, small body size or muscle mass may lead to higher blood concentrations after a given dose.

Documented subgroup pharmacodynamic differences are fewer, but have been observed, including increased sensitivity to beta-blockers in Asians, decreased sensitivity to beta-blockers in the elderly, decreased responsiveness to the blood pressure-lowering effects of adrenocortical extract (ACE) inhibitors and beta-blockers in African-Americans, and increased sensitivity to the central nervous system effects of midazolam in older people.

Despite the many examples of documented pharmacokinetic and pharmacodynamic differences in population subsets, there has often been insufficient attention in the course of drug development to looking for such differences among individuals in responses to drugs, including differences related to gender. In the case of gender, some have suggested the lack of information may have resulted from the exclusion of women from clinical trials. A number of studies have evaluated this possibility.

In 1983 and 1989, FDA examined the relative numbers of individuals from two important demographic groups, women and the elderly, in the data bases of new drug applications (NDA's). FDA found, in general, that the proportions of women and men included in the clinical trials were similar to the respective proportions of women and men who had the diseases for which the drugs were being studied, taking into account the age range of the population studied. The General Accounting Office (GAO) conducted a larger study of drugs approved during the period 1988 through 1991, with generally similar findings. Thus, women typically represent a majority of patients in NDA data bases of drugs used to treat conditions more common (or more commonly treated) in women (e.g., arthritis and depression) and a minority, although usually a sizable one of about 30 percent or more, in conditions that occur predominantly in males in the age ranges usually included in clinical trials (e.g., angina pectoris). Appendix I of the guideline includes additional details of these surveys.

Although women have been included in the later phases of clinical trials, inclusion alone is not sufficient for adequate assessment of potential gender differences. There must be an effort to use the data to discover such differences. An FDA guideline issued in 1988 ("Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications") called for analyses of gender-related differences in response. FDA and GAO examined NDA's to see whether analyses of this kind were being conducted and submitted. Both examinations found that in many cases (about half) the data bases were not being analyzed to determine whether there were gender, age, or race differences in response to drugs.

A further reason for the lack of information about potential gender differences in drug response is the lack of specific studies of pharmacokinetics in women, even where gender-related differences in pharmacokinetics might be expected or important. There are a variety of potential differences of this type, including differences due to menopause or the menstrual cycle, or to concomitant oral contraceptive or estrogen use, as well as differences based on different body fat proportion, and differences in weight or muscle mass.

C. FDA Guidance on Individualization of Treatment

Since 1988, FDA has taken several major steps to encourage development of data that support informed individualization of treatment:

1. The agency's 1988 guideline entitled, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications," calls for analyses of NDA data to identify variations among population subsets in favorable responses (effectiveness) and unfavorable responses (adverse reactions) to drugs. The population subsets that should be evaluated routinely include demographic subsets, such as different genders, age groups and races, people receiving other drug therapy, and people with concomitant illness.

2. The agency has addressed specifically the need to develop information on a particular demographic subset, the elderly, in the 1989 guideline entitled, "Guideline for the Study of Drugs Likely to be Used in the Elderly."

3. In the **Federal Register** of November 1, 1990 (55 FR 46134), the agency proposed to amend the labeling regulation (21 CFR 201.57) to require a "Geriatric Use" section that would contain available information on experience with the drug in the elderly and describe any needed modifications in the use of the drug in that population. In the **Federal Register** of October 16, 1992 (57 FR 47423), the agency proposed to amend the same regulation to facilitate inclusion of information on the use of drugs in children.

D. Changes in the Guideline

The new guideline discusses FDA's expectations regarding inclusion of patients of both genders in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and, where appropriate, assessment of pharmacodynamic differences and the conduct of specific additional studies in women. The policy applies to all drug or disease specific clinical guidelines based on the 1977 guideline, that exclude women of childbearing potential from participation in early studies of drugs.

III. Revised Policy on Inclusion of Women of Childbearing Potential in Clinical Trials

A. The 1977 Guideline—"General Considerations for the Clinical Evaluation of Drugs"

The 1977 guideline set forth a policy on, among other things, the inclusion of women of childbearing potential in clinical trials. The policy stated that, in general, women of childbearing potential should be excluded from the earliest studies of a new drug, that is, phase 1 and early phase 2 studies. Phase 1 refers to the first introduction of a new drug into humans, who are often, but not always, healthy volunteers, to study the basic tolerability of the drug, its metabolism, and its short-term pharmacokinetics. With the exception of some early studies in life-threatening diseases, phase 1 studies usually do not have therapeutic intent. Phase 2 refers to the initial controlled trials of a drug to study its effectiveness. Before the first such study, there is generally no evidence that the drug is of therapeutic value in humans.

If adequate information on effectiveness and relative safety were amassed during phase 1 and early phase 2, the guideline stated that women of

childbearing potential could be included in subsequent studies of effectiveness, that is, later phase 2 and phase 3 studies, so long as animal teratogenicity and the female part of animal fertility studies had been completed. The policy did not specifically address the manner in which the early human evidence of safety and effectiveness and the results of animal reproduction studies should be used to make decisions about participation of women in later trials, leaving these considerations to the usual risk-benefit assessment made by the patient, physician, and IRB, with subsequent FDA review.

In the 1977 guideline, the term "women of childbearing potential" was defined very strictly, essentially referring to all premenopausal women physiologically capable of becoming pregnant, including women on oral, injectable, or mechanical contraceptives, single women, celibate women, and women whose partners had been sterilized by vasectomy. There was no provision for the use of pregnancy testing to identify women who could participate in studies without a risk of fetal exposure. The 1977 guideline also noted, however, that women of childbearing potential could receive investigational drugs in the earliest phases of testing, even in the absence of adequate reproduction studies in animals, when the drugs were intended for life-saving or life-prolonging treatment.

The effect of the 1977 guideline has been that women generally have not been included in phase 1 nontherapeutic studies or in the earliest controlled effectiveness studies (i.e., early phase 2), except for studies of life-threatening illnesses, such as acquired immune deficiency syndrome (AIDS) and cancer.

B. Reasons for Revising the 1977 Policy

The policy set forth in the 1977 guideline has been under discussion for several years within and outside the agency, and there has been increasing sentiment that it should be revised. For example, in October 1992, FDA and the Food and Drug Law Institute cosponsored a meeting on women in clinical trials of FDA-regulated products at which many speakers described the current restrictions as paternalistic and overprotective, denying young women the opportunity available to men and older women to participate in early drug development research.

Although the 1977 guideline has not resulted in a failure to include adequate numbers of women in the later phases of clinical trials, it has restricted the early accumulation of information about response to drugs in women that could be utilized in designing phase 2 and 3 trials, and has perhaps delayed appreciation of gender-related variation in drug effects. The early exclusion also may have perpetuated, in a subtle way, a view of the male as the primary focus of medicine and drug development, with women considered secondarily. There is reason to believe that earlier participation of women in studies would increase the likelihood that gender-specific data might be used to make appropriate adjustments in larger clinical studies (e.g., different doses in women or weight adjusted (milligram per kilogram) dosing instead of fixed doses).

The agency believes that removal of the prohibition on participation of women of childbearing potential in phase 1 and early phase 2 trials is consistent with congressional efforts to prevent unwarranted discrimination against such women. For example, in the employment context, the Pregnancy Discrimination Act, as interpreted by the U.S. Supreme Court in the landmark case of *International Union, United Automobile, Aerospace and Agricultural Implement Workers, UAW* v. *Johnson Controls, Inc.*, 111 S.Ct. 1196 (1991), prohibits the blanket exclusion of pregnant women from jobs they are qualified to perform solely because the working conditions of those jobs pose potential risks to exposed fetuses. The Court emphasized that "decisions about the welfare of future children must be left to the parents who conceive, bear, support, and raise them, rather than to the employers who hire those parents." While the purposes of clinical trials to develop safe and effective drugs are manifestly different from the purposes of private employment, FDA takes serious note of the Court's position on a woman's right to participate in decisions about fetal risk and believes it is appropriate to consider the Court's opinion in developing policy on the inclusion of women in clinical trials.

C. Current FDA Position on Participation of Women of Childbearing Potential in Early Clinical Studies

The agency has reconsidered the 1977 guideline and has concluded that it should be revised. This does not reflect a lack of concern for potential fetal exposure or indifference to potential fetal damage, but rather the agency's opinion that (1) exclusion of women from early trials is not medically necessary because the risk of fetal exposure can be minimized by patient behavior and laboratory testing, and (2) initial determinations about whether that risk is adequately addressed are properly left to patients, physicians, local IRB's, and sponsors, with appropriate review and guidance by FDA, as are all other aspects of the safety of proposed investigations.

The agency is, therefore, withdrawing the restriction on the participation of women of childbearing potential in early clinical trials, including clinical pharmacology studies (e.g., dose tolerance, bioavailability, and mechanism of action studies), and early therapeutic studies. It is expected that, in accordance with good medical practice, appropriate precautions against becoming pregnant and exposing a fetus to a potentially dangerous agent during the course of study will be taken by women participating in clinical trials. It is also expected that women will receive adequate counseling about the importance of such precautions, that efforts will be made to be sure that a woman entering a trial is not pregnant at the time the trial begins (i.e., a pregnancy test detecting the beta subunit of the hCG molecule is negative), and that the woman participant is fully informed about the current state of the animal reproduction studies and any other information about the teratogenic potential of the drug. As is the case for all studies carried out under an investigational new drug application (IND), the adequacy of the precautions taken will be considered by FDA in its review of protocols. In situations where enrollment continues over a prolonged period (unlikely for early clinical studies) and significant new information about teratogenicity becomes available, the sponsor has the responsibility to transmit this information quickly to the investigator and to current as well as potential study participants in the informed consent process.

The agency recognizes that this change in FDA's policy will not, by itself, cause drug companies or IRB's to alter restrictions they might impose on the participation of women of childbearing potential. We do not at this time perceive a regulatory basis for requiring routinely that women in general or women of childbearing potential be included in particular trials, such as phase 1 studies. However, as this guideline delineates, careful characterization of drug effects by gender is expected by the agency, and FDA is determined to remove the unnecessary Federal impediment to inclusion of women in the earliest stages of drug development. The agency is confident that the interplay of ethical, social, medical, legal and political forces will allow greater participation of

women in the early stages of clinical trials.

In some cases, there may be a basis for requiring participation of women in early studies. When the disease under study is serious and affects women, and especially when a promising drug for the disease is being developed and made available rapidly under FDA's accelerated approval or early access procedures, a case can be made for requiring that women participate in clinical studies at an early stage. When such a drug becomes available under expanded access mechanisms (for example, treatment IND or parallel track) or is marketed rapidly under subpart E procedures (because an effect on survival or irreversible morbidity has been shown in the earliest controlled trials), it is medically important that a representative sample of the entire population likely to receive the drug has been studied, including representatives of both genders. Under these circumstances, clinical protocols should not place unwarranted restrictions on the participation of women.

The agency advises that this guideline represents its current position on the clinical evaluation of drugs in humans. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

IV. Comments

Interested persons may, on or before November 19, 1993, submit to the Dockets Management Branch (address above) written comments regarding this guideline. Two copies of any comments should be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. These comments will be considered in determining whether further amendments to, or revisions of, the guideline are warranted.

The new guideline replaces that portion of the 1977 guideline that dealt with women of childbearing potential. The text of the new guideline on gender differences follows:

Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs

I. Introduction

The Food and Drug Administration (FDA) advises that this guideline represents its current position on the clinical evaluation of drugs in humans. This guideline does not bind the agency, and it does not create or confer any rights, privileges, or benefits for or on any person.

The principles of inclusion of women in product development programs and analysis of subgroup differences outlined in this guideline also apply to the clinical development of biological products and medical devices.

A. Abstract

In general, drugs should be studied prior to approval in subjects representing the full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave qualitatively similarly in demographic (age, gender, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many quantitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse effect. Recognition of these differences can allow safer and more effective use of drugs. Rarely, there may be qualitative differences as well. It is very difficult to evaluate subsets of the overall population as thoroughly as the entire population, but sponsors are expected to include a full range of patients in their studies, carry out appropriate analyses to evaluate potential subset differences in the patients they have studied, study possible pharmacokinetic differences in patient subsets, and carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, are suggested by existing data, or that would be particularly important if present. Study protocols are also expected to provide appropriate precautions against exposure of fetuses to potentially dangerous agents. Where animal data suggest possible effects on fertility, such as decreased sperm production, special studies in humans may be needed to evaluate this potential toxicity.

B. Underlying Observations

The following general observations and conclusions underlie the recommendations set forth in this guideline:

1. Variations in response to drugs, including gender-related differences, can arise from pharmacokinetic differences (that is, differences in the way a drug is absorbed, excreted, metabolized, or distributed) or pharmacodynamic differences (i.e., differences in the pharmacologic or clinical response to a given concentration of the drug in blood or other tissue).

2. Gender-related variations in drug effects may arise from a variety of sources. Some of these are specifically associated with gender, e.g., effects of endogenous and exogenous hormones. Gender-related differences could also arise, however, not because of gender itself, but because the frequency of a particular characteristic (for example, small size, concomitant hepatic disease or concomitant drug treatment, or habits such as smoking or alcohol use) is different in one gender, even if the characteristic could occur in either gender. Proper management of patients of both genders thus requires that physicians know all the factors that can influence the pharmacokinetics of a drug. An approach is needed that will identify, better than is done at present, all such factors. Understanding how various factors may influence pharmacokinetics will greatly enhance our ability to treat people of both genders appropriately.

3. For a number of practical and theoretical reasons, the evaluation of possible gender-related differences in response should focus initially on the evaluation of potential pharmacokinetic differences. Such differences are known to occur and have, at least to date, been documented much more commonly than documented pharmacodynamic differences. Moreover, pharmacokinetic differences are relatively easy to discover. Once reliable assays are developed for a drug and its metabolites (such assays are now almost always available early in the development of the drug), techniques exist for readily assessing gender-related or other subgroup-related pharmacokinetic differences.

Formal pharmacokinetic studies are one means of answering questions about specific subgroups. Another approach is use of a screening procedure, a "pharmacokinetic screen" (see "Guideline for the Study of Drugs Likely To Be Used in the Elderly"). Carried out in phase 2 and 3 study populations, the pharmacokinetic screen can greatly increase the ability to detect pharmacokinetic differences in subpopulations and individuals, even when these differences are not anticipated. By obtaining a small number of blood concentration determinations in most or all phase 2 and 3 patients, it is possible to detect markedly atypical pharmacokinetic behavior in individuals, such as that seen in slow metabolizers of debrisoquin, and pharmacokinetic differences in population subsets, such as patient populations of different gender, age, or race, or patients with particular underlying diseases or

concomitant therapy. The screen may also detect interactions of two factors, e.g., gender and age. The relative ease with which pharmacokinetic differences among population subsets can be assessed contrasts with the difficulty of developing precise relationships of most clinical responses to drug dose or to the drug concentration in blood, which usually would be necessary when attempting to observe pharmacodynamic differences between two subgroups.

A final reason to emphasize pharmacokinetic evaluation is that it must be carried out to allow relevant assessment of pharmacodynamic differences or relationships. Assessing pharmacodynamic differences between groups or establishing blood concentration-response relationships is possible only when groups are reasonably well matched for blood concentrations. Enough pharmacokinetic data must therefore be available to permit the investigator to administer doses that will produce comparable blood concentrations in the subsets to be compared or, alternatively, to compare subsets that have been titrated to similar blood concentrations.

4. The number of documented gender-related pharmacodynamic differences of clinical consequence is at this time small, and conducting formal pharmacodynamic/effectiveness studies to detect them may be difficult, depending on the clinical endpoint. Such studies are therefore not routinely necessary. The by-gender analyses of clinical trials that include both men and women, however, which are specified in the 1988 guideline entitled "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" are not difficult to carry out. Particularly if these analyses are accompanied by blood concentration data for each patient, they can detect important pharmacodynamic/effectiveness differences related to gender.

C. Inclusion of Both Genders in Clinical Studies

The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response. Although it may be reasonable to exclude certain patients at early stages because of characteristics that might make evaluation of therapy more difficult (e.g., patients on concomitant therapy), such exclusions should usually be abandoned as soon as possible in later development so that possible drug-drug and drug-disease interactions can be detected. Thus, for example, there is ordinarily no good reason to exclude women using oral contraceptives or estrogen replacement from trials. Rather, they should be included and differences in responses between them and patients not on such therapy examined. Pharmacokinetic interaction studies (or screening approaches) to look at the interactions resulting from concomitant treatment are also useful.

Ordinarily, patients of both genders should be included in the same trials. This permits direct comparisons of genders within the studies. In some cases, however, it may be appropriate to conduct studies in a single gender, e.g., to evaluate the effects of phases of the menstrual cycle on drug response.

Although clinical or pharmacokinetic data collected during phase 3 may provide evidence of gender-related differences, these data may become available too late to affect the design and dose-selection of the pivotal controlled trials. Inclusion of women in the earliest phases of clinical development, particularly in early pharmacokinetic studies, is, therefore, encouraged so that information on gender differences may be used to refine the design of later trials. Note that the strict limitation on the participation of women of childbearing potential in phase 1 and early phase 2 trials that was imposed by the 1977 guideline entitled, "General Considerations for the Clinical Evaluation of Drugs," has been eliminated.

There is no regulatory or scientific basis for routine exclusion of women from bioequivalence trials. For certain drugs, however, it is possible that changes during the menstrual cycle may lead to increases in intra-subject variability. Such variability could be related to hormonally-mediated differences in metabolism or changes in fluid balance. Sponsors of bioequivalence trials are encouraged to examine available information on the pharmacokinetics and metabolism of the test drugs and related drugs to determine whether there is a basis for concern about variability in pharmacokinetics during the menstrual cycle. Where the available information does raise such concern, measures could be taken to reduce or adjust for variability, e.g., administration of each drug at the same phase of the menstrual cycle, or inclusion of larger numbers of subjects. Sponsors are encouraged to collect data that will contribute to the understanding of the relationship between hormonal variations and pharmacokinetics.

D. Analysis of Effectiveness and Adverse Effects by Gender

FDA's guideline on the clinical and statistical sections of NDA's calls for analyses of effectiveness, adverse effects, dose-response, and, if available, blood concentration-response, to look for the influence of: (1) Demographic features, such as age, gender, and race; and (2) other patient characteristics, such as body size (body weight, lean body mass, fat mass), renal, cardiac, and hepatic status, the presence of concomitant illness, and concomitant use of drugs, including ethanol and nicotine. Analyses to detect the influence of gender should be carried out both for individual studies and in the overall integrated analyses of effectiveness and safety. Such analyses of subsets with particular characteristics can be expected to detect only relatively large gender-related differences, but in general, small differences are not likely to be clinically important. The results of these analyses may suggest the need for more formal dose-response or blood concentration-response studies in men or women or in other patient subsets. Depending on the magnitude of the findings, or their potential importance (e.g., they would be more important for drugs with low therapeutic indices), these additional studies might be carried out before or after marketing.

E. Defining the Pharmacokinetics of the Drug in Both Genders

The factors most commonly having a major influence on pharmacokinetics are renal function, for drugs excreted by the kidney, and hepatic function, for drugs that are metabolized or excreted by the liver; these should be assessed directly as part of the ordinary development of drugs. The pharmacokinetic effects of other subgroup characteristics such as gender can be assessed either by a pharmacokinetic screening approach, described in the 1989 guideline entitled, "Guideline for the Study of Drugs Likely to Be Used in the Elderly," or by formal pharmacokinetic studies in specific gender or age groups.

Using either a specific pharmacokinetic study or a pharmacokinetic screen, the pharmacokinetics of a drug should be defined for both genders. In general, it is prudent to at least carry out pilot studies to look for major pharmacokinetic differences before conducting definitive controlled trials, so that differences that might lead to the

need for different dosing regimens can be detected. Such studies are particularly important for drugs with low therapeutic indices, where the smaller average size of women alone might be sufficient to require modified dosing, and for drugs with nonlinear kinetics, where the somewhat higher milligram per kilogram dose caused by a woman's smaller size could lead to much larger differences in blood concentrations of drug. Gender may interact with other factors, such as age. The potential for such interactions should be explored.

Three pharmacokinetic issues related specifically to women that should be considered during drug development are: (1) The influence of menstrual status on the drug's pharmacokinetics, including both comparisons of premenopausal and postmenopausal patients and examination of within-cycle changes; (2) the influence of concomitant supplementary estrogen treatment or systemic contraceptives (oral contraceptives, long-acting progesterone) on the drug's pharmacokinetics; and (3) the influence of the drug on the pharmacokinetics of oral contraceptives. Which of these influences should be studied in a given case would depend on the drug's excretion, metabolism, and other pharmacokinetic properties, and on the steepness of the dose-response curve.

Hormonal status during the menstrual cycle may affect plasma volume and the volume of distribution (and thus clearance) of drugs. The activity of certain cytochrome P450 enzymes may be influenced by estrogen levels and, in addition, microsomal oxidation by these enzymes may decline in the elderly more in men than women. Oral contraceptives can cause decreased clearance of drugs (e.g., imipramine, diazepam, chlordiazepoxide, phenytoin, caffeine, and cyclosporine), apparently by inhibiting hepatic metabolism. They can also increase clearance by inducing drug metabolism (e.g., of acetaminophen, salicylic acid, morphine, lorazepam, temazepam, oxazepam, and clofibrate). Certain anticonvulsants (carbamazepine, phenytoin) and antibiotics (rifampin) can reduce the effectiveness of oral contraceptives. Many of the potential interactions of gender and gender-related characteristics (e.g., use of oral contraceptives) can be evaluated with the pharmacokinetic screen. In some cases, specific studies will be needed.

F. Gender-Specific Pharmacodynamic Studies

Because documented demographic differences in pharmacodynamics appear to be relatively uncommon, it is not necessary to carry out separate pharmacodynamic/effectiveness studies in each gender routinely. Evidence of such differences should be sought, however, in the data from clinical trials by carrying out the by-gender analyses suggested in the guideline on the clinical and statistical sections of NDA's. These analyses of controlled trials involving both genders are probably more likely to detect differences than studies carried out entirely in one gender. Experience has shown that gender differences can be detected with such approaches.

If the by-gender analyses suggest gender-related differences, or if such differences would be particularly important, e.g., because of a low therapeutic index, additional formal studies to seek such differences between the blood level-response curves of men and women should be conducted. Even in the absence of a particular concern based on the by-gender analyses, if there is a readily measured pharmacodynamic endpoint, such as blood pressure or rate of ventricular premature beats, and if there are good dose-response data for the overall population, it should be feasible to develop dose response data from population subsets (e.g., both genders) in the critical clinical trials.

G. Precautions in Clinical Trials Including Women of Childbearing Potential

Appropriate precautions should be taken in clinical studies to guard against inadvertent exposure of fetuses to potentially toxic agents and to inform subjects and patients of potential risk and the need for precautions. In all cases, the informed consent document and investigator's brochure should include all available information regarding the potential risk of fetal toxicity. If animal reproductive toxicity studies are complete, the results should be presented, with some explanation of their significance in humans. If these studies have not been completed, other pertinent information should be provided, such as a general assessment of fetal toxicity in drugs with related structures or pharmacologic effects. If no relevant information is available, the informed consent should explicitly note the potential for fetal risk.

In general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of childbearing potential, i.e., usually by the end of phase 2 and before any expanded access program is implemented.

Except in the case of trials intended for the study of drug effects during pregnancy, clinical protocols should also include measures that will minimize the possibility of fetal exposure to the investigational drug. These would ordinarily include providing for the use of a reliable method of contraception (or abstinence) for the duration of drug exposure (which may exceed the length of the study), use of pregnancy testing (beta HCG) to detect unsuspected pregnancy prior to initiation of study treatment, and timing of studies (easier with studies of short duration) to coincide with, or immediately follow, menstruation. Female subjects should be referred to a study physician or other counselor knowledgeable in the selection and use of contraceptive approaches.

H. Potential Effects on Fertility

Where abnormalities of reproductive organs or their function (spermatogenesis or ovulation) have been observed in experimental animals, the decision to include patients of reproductive age in a clinical study should be based on a careful risk-benefit evaluation, taking into account the nature of the abnormalities, the dosage needed to induce them, the consistency of findings in different species, the severity of the illness being treated, the potential importance of the drug, the availability of alternative treatment, and the duration of therapy. Where patients of reproductive potential are included in studies of drugs showing reproductive toxicity in animals, the clinical studies should include appropriate monitoring and/or laboratory studies to allow detection of these effects. Long-term followup will usually be needed to evaluate the effects of such drugs in humans.

Appendix I

I. Surveys of Participation of Women in Clinical Trials in New Drug Applications (NDA's)

The extent of participation of women in the data bases of NDA's has been examined several times in recent years, by FDA in 1983 and 1989, and by the General Accounting Office (GAO) in 1992. In general, the genders were represented to approximately the extent one would predict from the gender prevalence of the condition treated by the drug in the age group studied. The relative disease prevalence in men and women can vary with age. Consider, for example, the participation of women in studies of anti-anginal drugs. Almost all patients in angina studies, which require vigorous treadmill exercise tests, are under 75 years old and the large

majority are under 65. Although eventually women develop symptomatic coronary artery disease in their 60's, 70's, and 80's, and become similar to men in the prevalence of this condition, they are much less likely than men to be affected in their 40's, 50's, and early 60's. The overall NDA data base for an anti-anginal drug, made up primarily of people 50 to 65, will therefore include a significantly greater proportion of men than women. Efforts to include more very old patients in trials, i.e., patients in their 70's and 80's, should lead to a greater proportion of women in trials of anti-anginal drugs.

Results of the FDA and GAO surveys are described below. Also included is an analysis of gender distribution in recently approved or submitted NDA's for antidepressant drugs. This analysis was conducted to evaluate the frequently heard claim that this class of drugs is studied predominantly (or even exclusively) in males despite the wide use of antidepressants in women.

A. The 1983 Survey

Primarily carried out to assess the inclusion of the elderly in NDA's, the 1983 survey looked at the age and gender prevalence of patients included in 11 pending NDA's. The NDA's were chosen because they were readily available and did not need to be retrieved from storage; figures were taken by FDA staff from the pending applications. In one case (ranitidine), the values represent only domestic patients for only one claim, leading to a small number of patients; many more patients (those included in foreign studies, or in studies of other claims) were available for safety evaluation.

Table 1 shows the results of the survey. As expected, the non-steroidal anti-inflammatory drugs (NSAID's) were studied predominantly in women, because arthritis, especially rheumatoid arthritis, is more common in women. This predominance was slightly less prominent in the case of zomepirac, which was studied extensively for pain (gender-neutral), in addition to arthritis. The hypnotic drug (triazolam) and the antibiotics (cefoperazone and netilmycin) were studied in approximately equal proportions of men and women. The patient populations included in the NDA's for verapamil for angina, and bumetanide, for heart failure, were about two-thirds male, and about two-thirds of the patients were less than 60 years old, an age group in which angina and heart failure are more prevalent in men than in women. In the patients over age 70, representing 10 percent of the bumetanide patients and 7 percent of verapamil patients, the gender distribution was about equal (49 percent women in the verapamil studies and 45 percent women in the bumetanide studies). Studies of ranitidine for duodenal ulcer, a predominantly male disease, included about 75 percent males. Other indications for this drug, such as gastric ulcer, would be expected to have a different gender distribution. The two anti-cancer drugs in this survey were studied principally for exclusively male conditions, cancer of the prostate and testis.

B. The 1989 Survey

In an effort to avoid possible selection bias, all drugs approved in 1988 were surveyed; this time the sponsors provided the data. FDA asked them to provide data reflecting "the principal data base used for safety review" in the latest safety update and asked that phase 1 subjects/patients be excluded. Sponsors gave either data on all patients or only patients given the test drug; the estimates of gender exposure should not be greatly affected by this difference.

Table 2 shows the results of the 1989 survey for 12 of the 20 drugs approved in 1988. Because sponsors had little control over gender distributions in the small populations available for study, four orphan drugs were omitted from the survey (tiopronin for prevention of cystine stones; ethanolamine oleate for esophageal varices; ifosfamide, third-line therapy for testicular cancer; and mesna, a prophylactic agent for ifosfamide-induced hemorrhagic cystitis). Also omitted were three contrast agents for single dose uses (but these agents are in the 1992 GAO survey), and a topical product (oxiconazole cream) for which gender distribution was not available.

Again, the anti-inflammatory drug (diclofenac) was studied predominantly in women (more than two-thirds of the patients), as was nimodipine, for prevention of vascular spasm after subarachnoid hemorrhage, also a female-predominant condition. Pergolide, an anti-Parkinson's disease drug; astemizole, an antihistamine; and octreotide, a drug for symptoms of carcinoid tumor, were studied in about equal numbers of men and women. The studies of the cardiovascular drugs nicardipine (angina and hypertension) and carteolol (hypertension) included 59 and 67 percent men, respectively, reflecting the male gender predominance of angina, and perhaps hypertension, in the relatively young (two-thirds of the patients were under the age of 60) populations studied. Nizatidine and misoprostol were studied extensively in duodenal ulcer, a predominantly male disease, with about 70 percent of patients being male, although approval of misoprostol was for a different claim. Cefotiam, an intravenous antibiotic, was studied mainly in elderly patients (65 percent over 60; 36 percent over 70); about two-thirds were male, for unclear reasons. The topicals were studied in a predominantly young population (about 90 percent under the age of 60), more often in males. Certain tinea infections (tinea cruris and tinea pedis) are more common in males, accounting for the high proportion (72 percent) of males in studies of naftifine. Why photoplex was studied somewhat more in males (63 percent) is not clear.

C. The GAO Survey

In 1992, the GAO analyzed the gender, age, and race distribution of all NDA's approved from January 1988 through June 1991. Data were collected by means of a questionnaire sent to the sponsor of each drug. The number of patients receiving the test drug during drug development, domestic studies only, was requested, and patients were broken down by gender, age (<15, 15 to 49, 50 to 64, >65), and race. The age distribution data allow a separate analysis of women of childbearing potential (taken here as women age 15 to 49). Data are available for 53 drugs (of 63 drugs approved during the 3 1/2-year period, 4 drugs intended for single gender use and 6 whose sponsors provided no, or no usable, questionnaire were omitted).

The results of the GAO survey are given in Tables 3A and 3B for phase 2 and 3 patients. The tables show gender distribution overall for the whole data base and for the 15 to 49 age group as well. For anti-inflammatory, anti-infective, central nervous system/anesthetic, topical, antihistamine, and cancer drugs, women constituted 40 percent or more of the patients studied, with occasional exceptions. The most striking exception is mefloquine, where only 11 percent of patients were women. This occurred because the primary studies of mefloquine for treatment of malaria were conducted in Thai military personnel. Women fairly consistently represented less than 40 percent of the patients for anti-ulcer drugs (duodenal ulcer, a male-predominant condition, was a principal disease studied for nizatidine, omeprazole, and misoprostol) but accounted for 55 percent of the patients in studies of dipentum, a drug for ulcerative colitis (ulcerative colitis is more common in women). Women consistently made up less than 40 percent of the populations studied for

cardiovascular disease, including populations used to evaluate agents used to diagnose or evaluate coronary artery disease, except for nimodipine (for spasm after subarachnoid bleed) and adenosine (for supraventricular tachycardia). For drugs to treat ventricular arrhythmias and angina, both commonly the result of coronary disease, the fraction of women ranged from 15 percent (bepridil, for unresponsive angina) to 20 to 30 percent (propafenone, moricizine, and indecainide), reflecting the lower rate of coronary artery disease in younger women and the fact that most patients in studies are under 60 years old. Studies of drugs for hypertension (carteolol, doxazosin, nicardipine, isradipine, ramapril, pinacidil) included 27 to 42 percent women. In some cases, these drugs were being evaluated for other claims, such as angina or heart failure, which are male predominant in the age groups studied. For all of the antihypertensives, there were at least 290 women in the domestic date base, enough to detect significant gender differences in response.

Of interest is the observation that there was no tendency for women to represent a lower percentage of patients in the 15 to 49 age group than in the overall population. There is thus no suggestion in these data that the restriction on participation of women of childbearing potential in early trials carries over to later phase 2 or 3 trials.

D. Antidepressants

By chance, none of the surveys included any antidepressant drugs, a class of drug frequently cited as needing study in women, both because women are frequently given antidepressants and because of suspected interactions of the drugs with the menstrual cycle.

Table 4 shows gender participation for sertraline and paroxetine, the two most recently approved antidepressants, as well as two agents likely to be approved within the next year. Women, as expected based on past experience, represented 58 to 65 percent of the patients.

II. Tables

TABLE 1

Drug	n	Percent of total	
		Female	Male
Anti-inflammatory:			
Benoxaprofen (Oraflex)	3,446	64	36
Ketoprofen (Orudis)	1,579	68	32
Zomepirac (Zomax)	3,479	60	40
Cardiovascular:			
Verapamil (Isoptin)	1,810	36	64
Bumetanide (Bumex)	838	27	72
Hypnotic:			
Triazolam (Halcion)	4,254	49	51
Antibiotic:			
Cefoperazone (Cefobid)	1,958	52	48
Netilmycin (Netromycin)	3,376	43	57
Anti-ulcer:			
Ranitidine (Zantac)	193	23	77
Anti-cancer (prostate, testes):			
Leuprolide (Lupron)	387	17	83
Etoposide (Vepesid)	259	16	84

TABLE 2

Drug	n	Percent of total	
		Female	Male
Anti-inflammatory:			
Diclofenac (Voltaren)	8,175	69	31
Cardiovascular/cerebrovascular:			
Nicardipine (Cardene)	2,962	41	59
Carteolol (Cartrol)	1,536	33	67
Nimodipine (Nimotop)	1,301	64	36
Anti-ulcer:			
Nizatidine (Axid)	2,063	31	69
Misoprostol (Cytotec)	8,687	28	72
Antibiotic:			
Cefotiam (Ceradon)	844	33	67
Anti-Parkinson:			
Pergolide (Permax)	1,836	45	55
Antihistamine:			
Astemizole (Hismanal)	1,356	48	52
Anti-carcinoid symptoms:			
Octreotide (Sandostatin)	455	49	51
Topical (tinea, sunscreen):			
Naftifine (Naftin)	452	28	72
Photoplex	227	37	63

TABLE 3A.— ALL AGES

Drug	n	Percent of total	
		Female	Male
Anti-inflammatory/Analgesic:			
Dezocine (Dalgan)	1,417	60	40
Diclofenac (Voltaren)	1,714	64	36
Etodolac (Lodine)	5,395	65	35
Ketorolac (Toradol)	1,248	64	36
Anti-infectives:			
Ofloxacin (Floxin)	3,585	56	44
Cefmetazole (Zefazone)	2,769	67	33
Cefixime (Suprox)	1,859	60	40
Fluconazole (Diflucan)	983	36	64
Naftifine (Naftin)	222	38	62
Cefpiramide	1,325	39	61
Mefloquine (Lariam)	1,319	11	89
Oxiconazole (Oxistat)	886	35	65
Central Nervous System/Anesthetic:			
Clomipramine (Anafranil)	3,826	54	46
Propofol (Dipravan)	696	48	52
Clozapine (Clozaril)	581	37	63
Estazolam (Prosan)	1,243	50	50
Pipecuronium (Arduan)	580	52	48
Doxacurium (Nuromax)	987	39	61
Pergolide (Permax)	1,667	43	57
Cardiovascular:			
Nimodipine (Nimotop)	343	69	31
Adenosine (Adenocard)	109	48	52
Doxazosin (Cardura)	698	42	58
Pinacidil (Pindac)	1,774	36	64
Nicardipine (Cardene)	1,915	37	63
Benazepril (Lotensin)	2,130	32	68
Isradipine (Dynacirc)	1,842	27	73
Propafenone (Rhythmol)	3,328	30	70
Ramapril (Altace)	1,723	33	67
Carteolol (Cartrol)	1,253	28	72
Moricizine (Ethmozine)	1,017	21	79
Indecainide (Decabid)	761	23	77
Bepridil (Vascor)	884	15	85
Cancer:			
Octreotide (Sandostatin)	569	38	62
Carboplatin (Paraplatin)	2,214	77	23
Levamisole (Ergamisol)	1,038	48	52
Ondansetron (Zofran)	939	29	71
Diagnostics:			
Technescan Mag 3	160	43	57
Ioversol (Optiray)	1,101	45	55
Gadopentetate (Magnevist)	410	41	59
TC–99M Sestamibi (Cardolyte)	1,102	29	71
TC–99M Exametazime (Ceretec)	202	28	72
Iotralan (Osmovist)	545	31	69
Topicals:			
Photoplex	371	40	60
Fluticasone (Cutivate)	730	42	58
Halobetasol (Ultravate)	662	46	54
Metipranolol (Optipranolol)	465	53	47
Cefotiam (Ceradon)	715	34	66
Rev-Eyes	646	47	53
Gastrointestinal:			
Olsalazine (Dipentum)	98	55	45
Nizatidine (Axid)	3,854	35	65
Misoprostol (Cytotec)	1,917	37	63
Omeprazole (Losec)	2,189	26	74
Antihistamine:			
Astemizole (Hismanal)	979	41	59

TABLE 3B.—AGES 15 TO 49

Drug	n	Percent of total	
		Female	Male
Anti-inflammatory/Analgesic:			
Dezocine (Dalgan)	1,142	61	39
Diclofenac (Voltaren)	577	55	45
Etodolac (Lodine)	3,155	65	35
Ketorolac (Toradol)	NA	NA	NA
Anti-Infectives:			
Ofloxacin (Floxin)	2,890	60	40
Cefmetazole (Zefazone)	1,621	72	28
Cefixime (Suprox)	879	70	30
Fluconazole (Diflucan)	759	64	36
Naftifine (Naftin)	151	36	64
Cefpiramide	362	44	56
Mefloquine (Lariam)	1,189	9	91
Oxiconazole (Oxistat)	NA	NA	NA
Central Nervous System/Anesthetic:			
Clomipramine (Anafranil)	3,277	55	45
Propofol (Dipravan)	514	58	42
Clozapine (Clozaril)	510	35	65
Estazolam (Prosan)	784	42	58
Pipecuronium (Arduan)	263	57	43
Doxacurium (Nuromax)	623	37	63
Pergolide (Permax)	357	63	37
Cardiovascular:			
Nimodipine (Nimotop)	195	63	37
Adenosine (Adenocard)	62	43	57
Doxazosin (Cardura)	62	43	57
Pinacidil (Pindac)	682	37	63
Nicardipine (Cardene)	596	39	61
Benazepril (Lotensin)	602	27	73
Isradipine (Dynacirc)	692	27	73
Propafenone (Rhythmol)	604	46	54
Ramapril (Altace)	622	23	77
Carteolol (Cartrol)	410	24	76
Moricizine (Ethmozine)	193	31	69
Indecainide (Decabid)	94	44	56
Bepridil (Vascor)	93	13	8
Cancer:			
Octreotide (Sandostatin)	391	34	66
Carboplatin (Paraplatin)	563	70	30
Levamisole (Ergamisol)	195	50	50
Ondansetron (Zofran)	288	19	81
Diagnostics:			
Technescan Mag 3	101	47	53
Ioversol (Optiray)	370	51	49
Gadopentetate (Magnevist)	183	29	71
TC–99M Sestamibi (Cardolyte)	402	34	66
TC–99M Exametazime (Ceretec)	26	50	50
Iotralan (Osmovist)	327	34	66
Topicals:			
Photoplex	296	34	66
Fluticasone (Cutivate)	405	45	55
Halobetasol (Ultravate)	360	45	55
Metipranolol (Optipranolol)	70	41	59
Cefotiam (Ceradon)	NA	NA	NA
Rev-Eyes	531	47	53
Gastrointestinal:			
Olsalazine (Dipentum)	72	60	40
Nizatidine (Axid)	2,302	32	68
Misoprostol (Cytotec)	945	33	67
Omeprazole (Losec)	NA	NA	NA
Antihistamine:			
Astemizole (Hismanal)	NA	NA	NA

TABLE 4.—ALL AGES

Drug	Date	n	Percent of total	
			Female	Male
Sertaline (Zoloft)	1991	2,979	58	42

TABLE 4.—ALL AGES—Continued

Drug	Date	n	Percent of total	
			Female	Male
Paroxetine (Paxil)	1992	4,126	65	35
Pending No. 1	NA	2,181	62	38
Pending No. 2	NA	2,255	62	38

Dated: July 19, 1993.

David A. Kessler,

Commissioner of Food and Drugs.

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Federal Register

Tuesday
August 2, 1994

JONATHAN K. WILKIN, M.D.

Part II

Department of Health and Human Services

Food and Drug Administration

International Conference on Harmonisation; Guideline on Studies in Support of Special Populations: Geriatrics; Availability; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93D-0138]

International Conference on Harmonisation; Guideline on Studies in Support of Special Populations: Geriatrics; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled "Studies in Support of Special Populations: Geriatrics." The guideline was prepared by the Efficacy Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline is intended to reflect sound scientific principles for testing drugs in geriatric populations. The guideline provides useful information for sponsors submitting applications to both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER).

DATES: Effective August 2, 1994. Submit written comments at any time.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:
Regarding the guideline: Patrick J. Savino, Center for Drug Evaluation and Research (HFD-8), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1012.
Regarding the ICH: Janet J. Showalter, Office of Health Affairs (HFY-20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Manufacturers Association. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held on September 16, 1992, the ICH Steering Committee agreed that the draft tripartite guideline entitled "Studies in Support of Special Populations: Geriatrics" should be made available for comment. Subsequently, the draft guideline which published in the **Federal Register** of April 16, 1993 (58 FR 21082), was made available for comment by the European Commission and the Japanese Ministry of Health and Welfare, as well as by FDA, in accordance with their consultation procedures. At a meeting held on June 24, 1993, the comments were analyzed and the guideline was revised as necessary.

With this notice, FDA is publishing in final form a guideline entitled "Studies in Support of Special Populations: Geriatrics." This guideline has been endorsed by all ICH sponsors. The guideline provides useful information to sponsors submitting applications to both CDER and CBER. The guideline addresses harmonization in relation to clinical testing programs for drugs intended for use in medicines for the geriatric population, which is expected to increase significantly in the near future in Europe, Japan, and the United States. The use of drugs in the geriatric population requires special consideration due to the frequent occurrence of underlying diseases, concomitant drug therapy, and the consequent risks of drug interaction. The recommendations of this guideline do not materially differ from the recommendations of a 1989 CDER guideline entitled "Guideline for the Study of Drugs Likely to be Used in the Elderly." Although the ICH harmonized guideline provides much useful information for sponsors submitting applications to CDER and CBER, the 1989 document contains background and additional commentary not present in the harmonized guideline. For this reason, FDA intends to provide both the ICH harmonized guideline and the 1989 document when information is requested on the study of new drugs in a geriatric population.

Guidelines are generally issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, this guideline is not being issued under the authority of § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments will be periodically reviewed and, where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the final guideline follows:

Studies in Support of Special Populations: Geriatrics

I. Statement of Purpose

It is important to ensure that clinical testing programs are carried out according to harmonised guidelines based on agreed ethical and scientific principles so that the international development of valuable innovative drugs is achieved with maximum efficiency. Harmonisation in relation to medicines for geriatric populations is an important issue because the total population of the elderly will increase significantly in the coming years in Europe, Japan and the USA. The use of drugs in this population

)ires special consideration due to the uent occurrence of underlying diseases, Acomitant drug therapy and the consequent risk of drug interaction.

II. General Principle

Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug.

III. Scope of Guideline

This guideline is directed principally toward new Molecular Entities that are likely to have significant use in the elderly, either because the disease intended to be treated is characteristically a disease of aging (e.g., Alzheimer's disease) or because the popula' . . to be treated is known to include substantial numbers of geriatric patients (e.g., hypertension). The guideline applies also to new formulations and new combinations of established medicinal products when there is specific reason to expect that conditions common in the elderly (e.g., renal or hepatic impairment, impaired cardiac function, concomitant illnesses or concomitant medications) are likely to be encountered and are not already dealt with in current labelling. It likewise applies when the new formulation or new combination is likely to alter the geriatric patient's response (with regard to either safety/tolerability or efficacy) compared with that of the non-geriatric patient in a way different from previous rmulations. The guideline also applies to w uses that have significant potential pplicability to the elderly.

It is recommended that exemptions from the guideline be determined in advance either by sponsors or, where feasible, by the sponsor and drug registration authorities, based, e.g., on estimates of the disease prevalence by age or through examination of the age distribution of usage for other drugs of the same class or drugs used for the same indication.

IV. Definition of the Population

The geriatric population is arbitrarily defined, for the purpose of this guideline, as comprising patients aged 65 years or older. It is important, however, to seek patients in the older age range, 75 and above, to the extent possible. Protocols should not ordinarily include arbitrary upper age cutoffs. It is also important not to exclude unnecessarily patients with concomitant illnesses; it is only by observing such patients that drug-disease interactions can be detected. The older the population likely to use the drug, the more important it is to include the very old.

V. Clinical Experience

Geriatric patients should be included in the Phase 3 database (and in Phase 2, at the sponsor's option) in meaningful numbers. The geriatric subpopulation should be represented sufficiently to permit the omparison of drug response in them to that f younger patients. For drugs used in diseases not unique to, but present in, the elderly, a minimum of 100 patients would usually allow detection of clinically important differences. For drugs to treat relatively uncommon diseases, smaller numbers of the elderly would be expected. Where the disease to be treated is characteristically associated with aging (e.g., Alzheimer's disease) it is expected that geriatric patients will constitute the major portion of the clinical database.

The overall database of the dossier should be examined for the presence of age-related differences, e.g., in adverse event rates, in effectiveness, and in dose-response. If these relatively crude overview analyses show important differences, further evaluation may be needed.

The geriatric data used in the overview can come either from the inclusion of elderly patients in all or most of the main Phase 3 or Phase 2/3 studies or from studies conducted exclusively in geriatric patients, at the sponsor's option. Inclusion of both groups in the same studies has the advantage of allowing direct comparisons of younger and older patients using data collected in similar ways. Such comparisons are more difficult when separate studies of young and old patients are used. Certain assessments, however, e.g., studies of cognitive function, require special planning and can be best accomplished in separate studies.

VI. Pharmacokinetic Studies

Most of the recognized important differences between younger and older patients have been pharmacokinetic differences, often related to impairment of excretory (renal or hepatic) function or to drug-drug interactions. It is important to determine whether or not the pharmacokinetic behavior of the drug in elderly subjects or patients is different from that in younger adults and to characterize the effects of influences, such as abnormal renal or hepatic function, that are more common in the elderly even though they can occur in any age group. Information regarding age-related differences in the pharmacokinetics of the drug can come, at the sponsor's option, either from a Pharmacokinetic Screen (as described subsequently) or from formal pharmacokinetic studies, in the elderly and in patients with excretory functional impairment.

It is recognized that for certain drugs and applications (e.g., some topically-applied agents, some proteins) technical limitations such as low systemic drug levels may preclude or limit exploration of age-related pharmacokinetic differences.

A. Formal Pharmacokinetic Studies

Formal PK studies can be done either in healthy geriatric subjects or in patient volunteers with the disease to be treated by the drug.

The initial PK study can be a pilot trial of limited size conducted under steady-state conditions to look for sizable differences between older and younger subjects or patients. A larger, single-dose PK study of sufficient size to permit statistical comparisons between geriatric and younger subjects' or patients' pharmacokinetic profiles is also acceptable.

In either case, if large (i.e., potentially medically important) age-related differences are found, the initial PK study may need to be followed by a multiple-dose PK study of sufficient size to permit statistical comparisons (geriatric vs. younger) at steady-state.

B. Pharmacokinetic Screening Approach

Sponsors may opt, instead of conducting a separate PK evaluation of the elderly, to utilize a Pharmacokinetic Screen in conjunction with the main Phase 3 (and Phase 2, if the sponsor wishes) clinical trials program. This screening procedure involves obtaining, under steady-state conditions, a small number (one or two) of drug blood level determinations at "trough" (i.e., just prior to the next dose) or other defined times from sufficient numbers of Phase 2/3 clinical trials patients, geriatric and younger, to detect age-associated differences in pharmacokinetic behavior, if they are present. It is important to record time of dosing prior to blood concentration measurements, and relation of dosing to meals, and to examine the influence of demographic and disease factors, such as gender renal function, presence of liver disease, gastrointestinal disease or heart disease, body size and composition, and concomitant illnesses.

Small differences are unlikely to be of medical importance. Where the screen detects large differences, formal pharmacokinetic studies may be indicated unless the screen's results are sufficiently informative.

The advantage of a Pharmacokinetic Screen is that it can assess the effects, not only of age itself, but also of other factors associated with age (altered body composition, other drugs, concomitant illness) and their interactions.

VII. Pharmacokinetics in Renally or Hepatically Impaired Patients

Renal impairment is an aging-associated finding that can also occur in younger patients. Therefore, it is a general principle, not specific to these guidelines, that drugs excreted (parent drug or active metabolites) significantly through renal mechanisms should be studied to define the effects of altered renal function on their pharmacokinetics. Such information is needed for drugs that are the subject of this guideline but it can be obtained in younger subjects with renal impairment.

Similarly, drugs subject to significant hepatic metabolism and/or excretion, or that have active metabolites, may pose special problems in the elderly. Pharmacokinetic studies should be carried out in hepatically-impaired young or elderly patient volunteers.

If a Pharmacokinetic Screen approach is chosen by the sponsor (Section VI, see above), and if patients with documented renal impairment or hepatic impairment (depending on the drug's elimination pattern) are included and the results indicate no medically important pharmacokinetic difference, that information may be sufficient to meet this Geriatric Guideline's purpose.

VIII. Pharmacodynamic/Dose Response Studies

The number of age-related pharmacodynamic differences (i.e., increased or decreased therapeutic response, or side

effects, at a given plasma concentration of drug) discovered to date is too small to necessitate dose response or other pharmacodynamic studies in geriatric patients as a routine requirement. Separate studies are, however, recommended in the following situations:

•Sedative/hypnotic agents and other psychoactive drugs or drugs with important CNS effects, such as sedating antihistamines

•Where subgroup comparisons (geriatric versus younger) in the Phase 2/3 clinical trials database indicate potentially medically significant age-associated differences in the drug's effectiveness or adverse reaction profile, not explainable by PK differences

IX. Drug-Drug Interaction Studies

Such interactions are of particular importance to geriatric patients, who are more likely to be using concomitant medications than younger patients, but of course are not limited to this age group. Therefore it is a general principle, not specific to these guidelines, that in cases where the therapeutic range (i.e., range of toxic to therapeutic doses) of the drug or likely concomitant drugs is narrow, and the likelihood of the concomitant therapy is great, that specific drug-drug interaction studies be considered. The studies needed must be determined case-by-case, but the following are ordinarily recommended:

•Digoxin and oral anticoagulant interaction studies, because so many drugs alter serum concentrations of these drugs, they are widely prescribed in the elderly, and they have narrow therapeutic ranges.

•For drugs that undergo extensive hepatic metabolism, determination of the effects of hepatic-enzyme inducers (e.g., phenobarbital) and inhibitors (e.g., cimetidine).

•For drugs metabolized by cytochrome P–450 enzymes, it is critical to examine the effects of known inhibitors, such as quinidine (for cytochrome P–450 2D6) or ketoconazole and macrolide antibiotics (for drugs metabolized by cytochrome P–450 3A4). There is a rapidly growing list of drugs that can interfere with other drugs that metabolize, and sponsors should remain aware of it.

•Interaction studies with other drugs that are likely to be used with the test drug (unless important interactions have been ruled out by a Pharmacokinetic Screen).

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Michael R. Taylor,

Deputy Commissioner for Policy.

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